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A Snapshot of a Paradigm Shift in the Systemic Therapeutic of HBP Cancers, What to Do and Where to Go Next?

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1. Introduction

Hepatopancreatibiliary (HPB) cancer is a major health challenge due to the high disease load. An estimated 905,700 patients were diagnosed with, and 830,200 patients died from hepatic cancer in the world in 2020 [1]. Pancreatic cancer has been recognized as the 11th most common cancer globally, counting 458,918 new cases and leading to 432,242 deaths in 2018, according to GLOBOCAN 2018 estimates [2]. Fortunately, the management of hepatopancreaticobiliary (HPB) cancers has evolved remarkably over the past two decades due to the advancement of treatment concepts and options.

1.1. Hepatocellular Carcinoma (HCC)

Systemic therapies of advanced HCC have acquired major momentum and considerable breakthroughs in the last ten years. Systemic therapy has gradually emerged from one targeted agent in 2008 to over seven regimens as in 2022, involving combinational treatment in both first-line and second-line treatment. In particular, the use of immune checkpoint inhibitors (ICIs), namely the combination of atezolizumab and bevacizumab, or the tremelimumab-durvalumab, has become the standard first-line systemic therapy for HCC.

The advancement of systemic therapy has led to changes in treatment concepts in both early-stage and intermediate-stage HCC. For early-stage HCC, the adjuvant use of ICIs is being evaluated by randomized controlled studies in patients after hepatic resection. The readout of those clinical trials will potentially revolutionize the treatment paradigm of HCC. Neoadjuvant treatment with the incorporation of ICIs for operable HCC is also explored by phase I/II studies. For intermediate-stage HCC, the recent LAUCH study has shown that the addition of lenvatinib to transarterial chemoembolization (TACE) could improve the survival outcomes of patients. Further studies are required to identify the most optimal population for this combination. In

addition, the combination of TACE with ICIs is evaluated by the EMERALD-1 study.

The best regimen and optimal sequence of systemic therapy is another active research area that requires exploration. A paucity of clinical trials is underway in investigating the subsequent treatment in patients who experienced disease progression on ICIs, including the phase III trial IMbrave 251 (atezolizumab–lenvatinib/sorafenib combination in HCC previously treated with atezolizumab–bevacizumab), and a phase II trial studying cabozantinib after disease progression on ICI (NCT04588051).

1.2. Biliary Tract Cancers (BTCs)

BTCs used to be considered a malignancy with limited treatment options. A recent TOPAZ-1 clinical trial demonstrates that the combination of ICI, durvalumab, with standard chemotherapy, improves the overall survival of patients in the first-line setting. The above findings await validation by the KEYNOTE 966 phase III clinical trial comparing the ICI, pembrolizumab, to placebo in combination with standard gemcitabine-cisplatin chemotherapy.

For intra-hepatic cholangiocarcinoma (CCA), the disease burden in the liver may be amenable to locoregional therapy. Two phase II clinical trials in Asia and Europe show that selective internal radio-nuclide therapy (SIRT) with yttrium-90 is associated with responses and potentially improved survivals in a proportion of patients with intra-hepatic cholangiocarcinoma. In the second-line or beyond setting, the molecular profiling of BTCs has identified druggable targets. These include the isocitrate dehydrogenase (IDH) inhibitors for IDH1/2 mutated CCA [3,4], fibroblast growth factor receptor-2 (FGFR2) inhibitors for FGFR2 fusion CCA [5], human epidermal growth factor (ErbB) inhibitors [6], vascular endothelial growth factor (VEGF) inhibitors [7,8], MET inhibitors [9], tropomyosin receptor kinase (TRK) inhibitors for Neurotrophic Tyrosine Receptor Kinase (NTRK) fusions [10], the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib for BRAF-V600E mutation [11], RET inhibitors for RET fusion-positive tumors [12], mitogen-activated protein kinase (MAPK) inhibitors [13] and breast cancer gene (BRCA) inhibitors [14]. Ongoing clinical trials are evaluating the use of targeted agents, mainly the FGFR2 inhibitors, in the first-line setting.

1.3. Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC is generally more resistant to drug treatment. Most patients will develop resistance to chemotherapy within a short period. Recent clinical trial data may indicate the targeted agents may be feasible in a small proportion of patients, which include elpercatinib for RET fusion-positive tumors [12], larotrectinib and entrectinib for TRK fusion-positive tumors [15], and sotorasib for RAS G12C mutated tumors [16]. For patients with germline mutation of the BRCA 1 or 2 gene, Olaparib, the poly ADP ribose polymerase (PARP) inhibitor, could be used as maintenance therapy after chemotherapy treatment.

2. Conclusion

Although tremendous progress in treating HPB cancers has been made in the past two decades, there are still many rooms to optimize the therapeutic strategies. Our journal focuses on the epidemiology, early diagnostic approaches, prognosis, and multidisciplinary management of HCC, BTCs, and pancreatic cancer. We aim to provide a professional platform for authors in different areas to communicate and tackle the difficulties encountered while managing diseases to reduce mortality and improve patients' quality of life. Progress in liquid biopsy brings hope for early diagnosis and potentially increases life expectancy. Exploring individualized therapeutic strategies, identifying new molecular pathways, investigating combination regimens, and overcoming chemoresistance are also highly promising. We encourage review articles, research papers, case reports, and short communications on related topics. Our journal is also designed to highlight the knowledge and new evolution of various aspects of HPB cancer in patients' care and to address the scientific questions that are still challenging today but expected in the future, which may facilitate the advancement of novel therapies and bring the real hope to the patients.

Conflicts of Interest

The authors declare that there is no conflicts of interest.

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